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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,966	07/28/2003	Laura P. Hale	1579-852	2269

23117 7590 12/02/2009

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
12/02/2009	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte LAURA P. HALE

Appeal 2009-005189
Application 10/627,966
Technology Center 1600

Decided: December 2, 2009

Before DEMETRA J. MILLS, RICHARD M. LEBOVITZ, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving a claim to a method of inhibiting melanin synthesis in a patient's skin by administration of ZAG. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

"Zinc alpha-2-glycoprotein (ZAG) is a plasma glycoprotein that was named for its electrophoretic mobility and for its ability to be precipitated by Zn salts" (Spec. 1, ll. 10-11). According to the Specification, "ZAG has been detected immunohistochemically in normal secretory epithelial cells of breast, prostate, and liver, in salivary, bronchial, gastrointestinal, and sweat glands" (Spec. 1, ll. 14-16). The Specification states that "[t]he normal functions of ZAG are unclear, however ZAG has been isolated from the urine of human cancer patients with cachexia and can function as a lipid-mobilizing factor" (Spec. 2, ll. 12-14).

The Claims

Claims 2, 6, 12, and 13 are on appeal. Claim 2 is representative and reads as follows:

> 2. A method of inhibiting melanin synthesis in the skin of a patient comprising administering directly to said skin of said patient an amount of ZAG sufficient to effect said inhibition.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Poortmans, *The level of Zn-α_2-glycoprotein in normal human body fluids and kidney extract*, 71 J. LABORATORY & CLINICAL MEDICINE 807-811 (1968).

Freshney, *Culture of Animal Cells, A Manual of Basic Technique* 4 (1983).

Dermer, *Another Anniversary for the War on Cancer*, 12 BIO/TECHNOLOGY 320 (1994).

Trisha Gura, *Systems for Identifying New Drugs are Often Faulty*, 278 SCIENCE 1041-1042 (1997).

Lei, *Detection and Cloning of Epidermal Zinc-α_2-glycoprotein cDNA and Expression in Normal Human Skin and in Tumors*, 67 J. CELLULAR BIOCHEMISTRY 216-222 (1997).

The issue

The Examiner rejected claims 2, 6, 12, and 13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement (Ans. 3-9).

The Examiner finds that "no one of skill in the art would believe it more likely than not that the claimed invention would function as claimed and contemplated, that is inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition, based on the data provided" (Ans. 8).

Appellant argues that "[i]t is now well settled that a patent applicant enjoys the presumption that his/her invention can be practiced as claimed. The burden is on the examiner to provide evidence to the contrary. No such evidence has been provided here. Accordingly, reversal of the rejection based on lack of enablement is requested" (App. Br. 12).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Has Appellant demonstrated that the Examiner erred in finding that the claimed method of "inhibiting melanin synthesis in the skin" by administering ZAG is not adequately enabled by the Specification.

Findings of Fact (FF)

Breadth of the Claims

1. The Examiner finds that "claims are broadly drawn to a method of inhibiting melanin synthesis *in vivo* comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition. The claims encompass contacting any melanocyte in any location with an amount of ZAG sufficient to effect inhibition of melanin synthesis" (Ans. 3).

Direction, Guidance and Working Examples

2. The Specification teaches that "[*i*]*n vitro*, B16 melanoma cells typically produce melanin such that the culture supernatant turns visually black soon after cultures become confluent" (Spec. 14, ll. 25-26). The Specification teaches that B16 cells expressing ZAG at high levels showed that a "clear and consistent decrease in the rate of melanin accumulation could be seen within cultures . . . soon after cultures reached confluence" (Spec. 15, ll. 1-4).

3. The Specification teaches that "although B16-rhZAG clone 3G12 can produce (albeit decreased amounts of) melanin *in vitro*, tumors derived from these cells show no evidence of melanin production *in vivo* and thus appear white grossly" (Spec. 17, ll. 10-13). The Specification teaches that "[t]his marked decrease in melanin production by B16-rhZAG cells *in vivo* contrasts with the comparatively modest decrease in melanin production seen in these cells *in vitro*" (Spec. 17, ll. 15-17).

4. The Specification teaches that "addition of exogenous rhZAG also inhibited melanin production by B16-V cells *in vitro* in a dose-dependent fashion" (Spec. 16, ll. 22-24).

5. The Specification teaches that ZAG decreased melanin synthesis in melan-A cells, normal primary murine melanocytes, "in a dose-dependent fashion . . . these studies indicate that ZAG has similar effects on melanin production in both normal and malignant melanocytes" (Spec. 19, ll. 13-20).

State of the Art and Unpredictability of the Art

6. The Examiner finds that "(1) it is well known in the art that *in vitro* cultured cells have different characteristics than cells in the *in vivo* host animal and, additionally, (2) one cannot predict without undue experimentation the amount of ZAG sufficient to inhibit melanin synthesis by topical administration of ZAG *in vivo* given the known presence in the art of ZAG in the epidermis and in sweat which contacts the epidermis" (Ans. 5).

7. Freshney teaches that "cells from multicellular animals do not exist in isolation, and consequently, are not able to sustain independent existence without the provision of a complex environment, simulating blood plasma and insterstitial fluid" (Freshney 3, col. 2).

8. Dermer teaches that the "cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body" (Dermer 320, col. 1).

9. Dermer teaches that the "standard approach of most cancer scientists to experimentation produces little of practical value because it is flawed. Typically, an observation is first made in culture, then the

investigator turns to human cancer . . . An unnatural condition created in the laboratory is being mistaken for human cancer" (Dermer 320, col. 2).

10. Gura teaches that the "fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (Gura 1041, col. 1).

11. Gura teaches that "attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor sites" (Gura 1041, col. 1).

12. Poortmans teaches that ZAG "which is present in low concentration in serum, can be demonstrated in the external biological fluids tested here (urine, saliva, sweat)" (Poortmans 809).

13. Lei teaches that "[c]onvincing evidence that Zn$\alpha_2$gp is native to the epidermis (as against a contamination by skin gland secretions) is our success in cloning its cDNA from a library derived from cultured epidermal keratinocytes" (Lei 220, col. 1).

Principles of Law

"In order to satisfy the enablement requirement of section 112, an applicant must describe the manner of making and using the invention in such full, clear, concise, and exact terms as to enable any person skilled in the art … to make and use the same ….' 35 U.S.C. § 112, para. 1." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322 (Fed. Cir. 2005).

> Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the

> quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Analysis

The Specification provides particularized data which shows that ZAG reduces melanin levels in vitro and in an in vivo model system (FF 2-5). The Examiner addresses this specific data with two general concerns, that in vitro model systems are not reliable (FF 7-11) and that ZAG is normally expressed in epidermis (FF 12-13).

Neither of these arguments is persuasive. Even accepting that model systems are not entirely reliable, the examples provided by Appellant in the Specification provide specific evidence which shows the effect of ZAG on melanin levels in several different model systems. If we accepted the Examiner's argument that simply because model systems are unreliable, a method based upon such systems would require undue experimentation, patents would not issue until after phase 3 clinical trials by FDA. As

explained in *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995), the USPTO should not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." The Examiner has not provided a sound basis upon which to doubt the experimental results described in the Specification. The publications cited by the Examiner address cancer models generally, but not the specific melanin models utilized by Appellant.

The Examiner's second point, that ZAG is normally expressed in epidermis, and therefore "the effects of administration of additional ZAG cannot be predicted given the apparently ubiquitous and high expression of this secreted protein" (Ans. 7). First, the statement that there is "high expression" of secreted ZAG lacks any support in either Poortmans or Lei, neither of whom teach specific ZAG expression levels in epidermis (FF 12-13). Second, the argument that ZAG is normally expressed at some level does not logically mandate that addition of large amounts of exogenous ZAG would not cause different effects than the amounts naturally expressed by the body. Many compounds are normally expressed at particular levels in the body where addition of high levels of exogenous compound will cause significantly different effects, such as insulin, for example.

Balancing the *Wands* factors, we agree with Appellant that undue experimentation would not have been required to make and use the claimed invention.

Conclusion of Law

Appellant has demonstrated that the Examiner erred in finding that Specification description would require undue experimentation to enable a method of "inhibiting melanin synthesis in the skin" by administering ZAG as required by claim 2.

SUMMARY

In summary, we reverse the rejection of claims 2, 6, 12, and 13 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

REVERSED

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